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PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference X-16410	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/US2004/025593	International filing date *(day/month/year)* 25.08.2004	Priority date *(day/month/year)* 27.08.2003

International Patent Classification (IPC) or national classification and IPC
A61K31/138, A61K31/40, A61K31/4025, A61K31/4375, A61K31/4462, A61K31/4468, A61K31/4525, A61K31/453, A61K31/4704, A61K31/4709, A61K31/5375, A61K31/5377, A61P25/00

Applicant
ELI LILLY AND COMPANY et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 1 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.07.2005	16.12.2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/025593

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-282 as originally filed

   Claims, Numbers

   1-3 filed with telefax on 01.12.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☒ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☒ the claims, Nos. 4
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/025593

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-3
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-3
Industrial applicability (IA)	Yes:	Claims	1-3
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item I

Basis of the report

With his telefax of 01-12-05, the applicant has filed a new set of claims 1-3. These modifications do not introduce subject-matter which extends beyond the content of the original application, and thus fulfill the requirements of Art.34(2)(b) PCT.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D7: ANONYMOUS: "Medication Reference" INTERNET ARTICLE, [Online] 2 August 2003 (2003-08-02), XP002305149 Retrieved from the Internet: URL:http://web.archive.org/web/20030802202920/http://www.patientcenters.com/autism/n ews/med_reference.html> [retrieved on 2004-11-11]

D12: WO02070457 A 12 September 2002

D13: EP0721777 A 17 July 1996

V.1. Novelty

Claims 1-3 appear to be novel over the available prior art, since none of the cited prior art documents disclose the use of atomoxetine or a compound of formula I as sole active agents for the treatment of the specific pervasive developmental disorders listed in claim 1.

V.2. Inventive step

V.2.1. Claim 1:

Claim 1 does not appear to involve an inventive step in the sense of Article 33(3) PCT, the reasons being as follows:

a) D12, which is considered to represent the most relevant state of the art, discloses the use of compounds of formula I or metabolic precursors thereof for the treatment of disorders linked to decreased neurotransmission of serotonin and/or norepinephrine in mammals, such disorders including i.a. autism (p.2, l.4-21; p.17, l.4-14). The metabolic precursor is preferably the selective norepinephrine reuptake inhibitor atomoxetine hydrochloride (p.1, l.11; p.15, l.7 - p.16, l.3; p.17, l.20-28).

b) The subject-matter of claim 1 differs from D12 in that D12 does not mention other pervasive developmental disorders, such as Asperger's Disorder, Rett's Disorder, Childhood Disintegrative Disorder and Pervasive Developmental Disorder not otherwise specified.

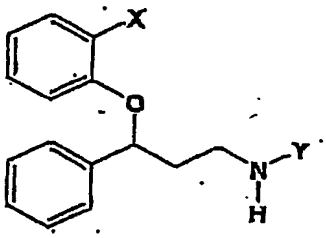
c) Nevertheless, it is known from D7 that selective norepinephrine reuptake inhibitors such as reboxetine are occasionally prescribed to people with autistic spectrum disorders (p.6, paragraphs 3 and 4). It may be argued that this disclosure does not provide a sufficiently strong incentive to the skilled person to select selective norepinephrine reuptake inhibitors in order to solve the technical problem of finding further means for the treatment of the pervasive developmental disorders listed in claim 1, in particular since D7 does neither explicitly recommend such use of reboxetine nor does it suggest its efficacy for this purpose. However, the skilled person being aware of the well-known fact that the symptomatology of autism and the other pervasive developmental disorders listed in claim 1 is very similar and that the differentiation of the different disorders can be quite problematic in clinical practice, would be prompted in light of the teaching of D12 taken alone or in combination with D7 to select norepinephrine reuptake inhibitors such as atomoxetine in order to treat further autistic spectrum disorders such as those listed in claim 1.

V.2.2. Claims 2, 3:

Dependent claims 2, 3 do not appear to contain any additional features which, in combination with the features of any claim to which it refers, meet the requirements of the PCT with respect to inventive step. In particular, in view of the fact that the use of atomoxetine for the treatment of attention deficit/hyperactivity disorder is known in prior art (D13), it would be obvious for the skilled person to select the aforementioned compound for the treatment of patients in which attention deficit/hyperactivity disorder occurs comorbidly with a pervasive developmental disorder.

We Claim:

1. Use of a norepinephrine reuptake inhibitor selected from the group consisting of atomoxetine and a compound of formula I:



wherein X is C_1-C_4 alkylthio, and Y is C_1-C_2 alkyl, or

a pharmaceutically acceptable salt thereof,

as sole active agent for the manufacture of a medicament for the treatment of a Pervasive Developmental Disorder selected from the group consisting of Asperger's Disorder, Rett's Disorder, Childhood Disintegrative Disorder, and Pervasive Developmental Disorder Not Otherwise Specified.

2. The use of claim 1, wherein Attention-Deficit Hyperactivity Disorder occurs comorbidly with said Pervasive Developmental Disorder.

3. The use of claim 1 or 2, wherein said norepinephrine reuptake inhibitor is atomoxetine hydrochloride.